REMARKS

Claims 1-101 are pending in the application, however claims 2, 10-12, 20, 25-32 and 34-101 are withdrawn as drawn to a non-elected invention. The Office has amended the requirement for restriction and indicated that claims group I and II (claims 1, 3-9, 13-19, 21-24 and 33) have been examined, however claims 10-11 and 28 also have been examined.

In reviewing the application, it has come to Applicants' attention that several typographical errors were present in the Sequence Listing, such that some sequences did not correspond to the sequences provided in the specification. Applicants are submitting with this response a substitute Sequence Listing with computer-readable form and paper copy. Changes are made to sequences 51, 56, 61 and 240 so that they are the same as the sequences provided in the specification with those sequence identifiers. Therefore no new matter is included. Applicants request that this substitute Sequence Listing be entered into the application. Applicants hereby state as required by 37 C.F.R. §§1.821(f), that the sequence information contained in the computer readable form and the paper copy is identical and contains no new matter.

The Office has indicated that the inventors' declaration is defective. Applicants submit herewith a newly executed declaration. Applicants therefore request that any objection to the inventors' declaration be withdrawn.

The Office has objected to the specification because it contains an embedded browser-executable code in paragraph 69. Applicants have amended the specification to delete this material and to correct other minor typographical errors. Applicants now request that any objections to the specification be withdrawn.

Claims 1, 3-11, 13-19, 21-24, 28 and 33 have been rejected as not enabled for a method using a biased library derived from

the carboxyl terminus of all types of Gα-coupled receptor. The Office reasons that the specification and Examples show how to identify an inhibitor using a known biased peptide library, but does not show applicability to GPCR in general, emphasizing that these receptors have different ligands such as hormones and viruses. The Office concludes that a skilled person would not consider the example provided to be predictive "to an unknown or unidentified receptor(s) of any GPCRT-binding ligand from a library of an infinite combinations of peptide and/or non-peptide compounds." As evidence, the Office notes that some analogs tested show no binding to the receptor while others have significant binding because a difference in one amino acid can substantially reduce the ability to bind.

This reasoning misses the point of the invention, which is, as recited in claim 1, a method of identifying a G protein coupled receptor signaling inhibitor. The invention is a <u>screening</u> assay method that allows one to identify desired compounds. Not all compounds subject to a screen will provide a positive result. In addition, the invention does not relate to methods using an infinite combination of <u>any</u> G protein coupled receptor <u>with</u> <u>any</u> library, but a finite combination of a G protein coupled receptor with a library based on sequences from a cognate G protein. The method can and does work with <u>any</u> G protein coupled receptor since the library used in each case is based on the sequence of the partner protein for the G protein coupled receptor, namely the G protein. G protein coupled receptors are so named because of their use of heterotrimeric G proteins to relay the signal from outside the cell into the cell. This protein-protein interaction between a G protein coupled receptor and a G protein is the basis for the screen. If one blocks the ability of the G protein coupled receptor to bind to

the G protein, the G protein coupled receptor can no longer send its normal signal effectively.

The test of enablement determines whether one skilled in the art could make or use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. The test is not whether <u>any</u> experimentation is necessary, but whether, if experimentation is necessary, it is beyond that which is considered routine by those practicing this art. The fact that experimentation may be complex does not necessarily make it "undue," if the normal practitioner in the art typically engages in such experimentation.

The Office specifically points to an alleged failure of the specification to provide adequate disclosure in the following areas: (1) how to determine which G proteins can be made into a library, which receptors can bind and which residues and candidate compounds can form the library; (2) working examples for <u>any</u> type of G proteins, its receptors and methods for making different libraries and expression vehicles; (3) expression vectors and levels suitable for all nucleic acids encoding peptides; (4) methods to avoid limitations in current techniques for using expression vectors; (5) methods to get around unpredictable effects on proper expression of various different combinations of amino acids; and (6) sufficient description to provide assurance of success of the claimed method since the art allegedly is generally unpredictable and numerous variables are undefined.

The present invention uses interference with binding between a G protein coupled receptor and its cognate G proteins, instead of using interference with binding between G protein coupled receptor and its extracellular ligands, to identify a specific inhibitor of a specific G protein coupled receptor. Thus one or

more peptides from a library of peptides, based on a G protein sequence from a G protein that binds to the G protein coupled receptor, mimics the G protein coupled receptor binding region of the G protein and inhibits or otherwise affects receptor-G protein interactions specifically and with high affinity.

The claims have been amended to clarify these points discussed above. The scope has not been narrowed by these amendments. Claim 1 now recites that the peptide library is "based on a native G protein sequence that binds to said G protein coupled receptor on an intracellular location of said G protein coupled receptor." Since G proteins have been cloned and sequenced, and since the prior art already has identified Gα and Gβγ regions that are implicated in G protein coupled receptor binding, it involves no experimentation to develop a library from any of these sequences according to the methods described in detail in the specification. See, for example, Azpiazn *et al.*, 1999 and Blakos *et al.*, 2001 (copies enclosed in accompanying Information Disclosure Statement) and Hamm, 1998 and Onrust, 1997 (already of record in this application); see also U.S. Patent Nos. 5,733,731 and 6,156,511 (copies enclosed in accompanying Information Disclosure Statement). The disclosure provides detailed teachings on how to produce a suitable library for screening peptides based on a known G protein sequence and explicitly states that this same methodology can be used for any region of Gα and Gβγ G protein subunits. Therefore, any skilled molecular biologist could, using the common knowledge in the field concerning G protein binding and sequence, along with what is disclosed in the application, make a library based on any G protein sequence known or later shown to bind a G protein coupled receptor.

The Office's first point does not pertain to this invention because any G protein can be used to base a peptide library on

its G protein coupled receptor binding sequence. The prior art shows a very large number of G protein coupled receptors and for many of them the G proteins to which they can bind. Even if it is not known if a particular pair of G protein and G protein coupled receptor can bind, it is a simple matter to perform a binding assay. Any competent graduate student or technician in the field could perform such an assay, so it could hardly be considered "undue" experimentation for a skilled molecular biologist. Once a G protein coupled receptor is chosen, therefore, it is a simple matter to either select from among the G proteins known to bind or to perform binding assays to select a previously unknown binder from among other G proteins. Once this is done, the specification shows how to make a library based on any desired sequence from the G protein. The methods shown work to produce a library based on any sequence. The Office has submitted no evidence whatsoever to cast doubt that the guidance provided beginning at paragraph 54 concerning how to make a library based on a known sequence using computer-generated random substitutions could not be used with "any protein known to interact with a GPCR, using randomly created overlapping regions of the protein." See ¶ 55 of the specification. Further, the specification provides, in Tables II and III, dozens of exemplary sequences obtained using several different libraries, each containing millions of peptide members. Therefore the Office's second point concerning working examples also was made in error.

The third point involves disclosure relating to expression vectors and levels. This invention is not performed *in vivo*, therefore the problems which have been noted with finding appropriate methods to express appropriate levels of peptide are not present here. Many expression vehicles are known in the art and are suitable for use *in vitro* with minimal and merely routine adjustments. A skilled person would have no trouble performing

these methods without undue experimentation even without any guidance. But the specification here does provide guidance and a specific system which does work. See, for example, Gilchrist *et al.*, 1999, already of record in this application. The Office has simply speculated based on a general understanding of the difficulties of expression of a peptide from vectors, for example for gene therapy, without providing any reasonable basis for such speculation.

The claimed invention does not claim a peptide library or library of candidate compounds per se, or a vector or expression system. Such libraries and vectors are known. The expression system used and described at length in the specification worked for the peptide library in question and successfully expressed a large number of peptides (see Examples 23-24). The Office has not provided any reason whatsoever that this system, which was used with several G protein sequence-based libraries (see ¶ 137), would not work equally well with any other library. Construction of vectors to express peptides that are designed based on a native G protein sequence to form a peptide library is within the knowledge of one skilled in the art and do not amount to undue experimentation. The examples provided involve use of multiple libraries, each of which contains preferably 10^9 peptides or more. See Examples 1-2. To assume that the skilled worker would be beset with "unpredictable effects on proper expression of various different combinations of amino acids" if the library is based on a different G protein sequence than those specifically exemplified here and that this would result in inability to perform the method, is simply not founded. This system has been show to work and to express at least one billion different peptides based on different G protein peptide sequences. The Office points 4-5 therefore also do not have merit with respect

to this invention and cannot properly from the basis of a rejection.

In the Office's sixth point, it is asserted that skilled artisans are provided little assurance of success in identifying an inhibitory peptide. The only reasoning given for this conclusory statement is that the art is unpredictable with regard to "numerous undefined variables" involved in the method. What these variables are and the unpredictable factors in the art which contribute to this are not communicated. Each panning example provided in the original disclosures resulted in not one but several high affinity peptide sequences. See, for example, Tables IX and X for two different conformations of rhodopsin with a Gt-based library, Table XI, XII and XIII for PAR1 with a Gq-based library using three different receptor sources, and Table XIV for a β_2-adrenergic receptor and a Gs-based library. See also the peptides identified and provided in Tables XV-XVII. In the absence of any reasonable explanation as to why the Office doubts the invention could be successful with any G protein coupled receptor and G protein that interacts with it, this rejection is not proper.

It was a matter of mere routine at the time this application was filed to select a G protein known to interact with a particular G protein coupled receptor or to identify one through elementary binding assays. It was a matter of mere routine at the time this application was filed to construct a peptide library from either any known sequence of such G proteins using a particular sequence previously known to bind or random overlapping sequences from the known complete sequence. It was a matter of mere routine at the time this application was filed to express these peptide libraries and would not have involved any experimentation, much less undue experimentation, to do so using the detailed guidance present in the specification an Examples.

Given the success of the methods using many different G protein coupled receptor/G protein library pairs incorporating many billions of different peptides screened, the skilled artisan would be assured that these methods would be successful as claimed.

Therefore, Applicants request that the rejection based on an asserted lack of enablement under the standards of 35 U.S.C. §112, first paragraph be withdrawn.

Claims 1, 3-11, 13-19, 21-24, 28 and 33 have been rejected under 35 U.S.C. §112, second paragraph as indefinite. The individual points raised by the Office are discussed in turn.

With respect to claim 1, the Office objects to a perceived omission of an essential step of "providing" the library. The claim as originally presented recites a first step of "providing a library based on a native G protein" and has been amended to clearly indicate the sequence binds to the G protein coupled receptor on an intracellular location. The claim also has been amended to provide a final "identifying" step. The Office had objected to the term "high," which has been deleted. The phrase "the native peptide" was considered to lack antecedent basis. Applicants believe that the amendments to this phrase in step (c) conform to the preamble. Applicants therefore request that the Office withdraw the rejection of claim 1 on grounds of indefiniteness.

With respect to claim 3, the Office specifically points to the phrase "at least an intracellular fragment." Applicants have canceled this phrase and rewritten this claim limitation for the sake of clarity and therefore request the indefiniteness rejection be withdrawn.

The Office also states that "at least two sequential binding assays" does not clearly set forth the metes and bounds of the numbers of assays. Applicants traverse this rejection. The term

"at least" is recognized by the Office as definite unless other claim terms or limitations introduce an ambiguity as to its meaning. In this case, the claim limitation is clear and clearly defines the number of sequential binding assays to be two assays or more. The reader does not have doubt that "at least two" sets forth the number of assays precisely and would have no trouble determining what number of assays fall within the claim. Simply because the claim is broad with respect to the number of assays included does not render the claim indefinite. See M.P.E.P. §§2173.04, 2173.05(c). Applicants request that this rejection be withdrawn as improper.

The Office also remarks that claims 14-17 are indefinite because they do not recite steps for the competition binding assay or the components involved. Applicants traverse this rejection. The term "competitive binding assay" is clear to one of skill in the art and does not introduce ambiguity in any way. The claim is intended to include all competitive binding assays that comport with the base claim and is not limited to assays having particular steps or particular components. Breadth of a claim does not make it indefinite. See M.P.E.P. §2173.094. Applicants believe this rejection is not proper and request its withdrawal.

Claims 18-19 are rejected as broadening the base claim because the base claim does not recite a detectable signal for each and every library member. Applicants do not understand this rejection. Claims 18 and 19 introduce a new limitation not present in either base claim and therefore are narrower than their respective base claims. The claims have been amended to address the Office's second point concerning the term "capable," which has been deleted. The claims currently recite methods of the base claim wherein library members provide a signal to detect binding. Applicants believe that claims 18-19 conform to the

standards of 35 U.S.C. §112, second paragraph, and therefore request the withdrawal of the rejection under that provision of the statute.

Claims 21-23 have been rejected for recitation of the phrase "activating ligand," which is deemed to be unclear. Claim 21 has been amended to avoid that specific terminology. Applicants therefore request that the Office withdraw the rejection of claims 21-23.

Claim 28 has been rejected as indefinite for use of the phrase "focussed library," which is asserted to be undefined. The claim recites not merely a focussed library, but a "focussed library of candidate compounds based on the structure of a compound selected in step (c)." Applicants traverse this rejection. The term "focussed" with respect to libraries is a well known term of art that would have been clear to any skilled person reading these claims at the time of filing. The further limitations to the claim discussed above also guides the reader to the exact meaning of this word in the claim. Applicants enclose three abstracts published close to the time of filing of this application which use the term focussed as evidence that this term was well understood by those in the art around the time this application was filed. See Adang and Humkins, Bala *et al.*, and Ley *et al.*, copies provided with accompanying Information Disclosure Statement.

Applicants believe that all claims comply with the requirements of 35 U.S.C. §112, second paragraph and request that the rejections under this statute be withdrawn.

Claims 1-11, 13-19, 21-24 and 33 have been rejected as obvious over either Coughlin *et al.* or Fowlkes *et al.* in view of Gilchrist under 35 U.S.C. §103.

The Office describes the disclosures of Coughlin *et al.* as relating to a method for identifying compounds that interact with

a cellular receptor using a library of compounds that bind to the receptor at the location an extracellular ligand binds to the receptor. Coughlin *et al.* teach a method for screening for compounds that act as a PAR3 ligand agonists or that inhibit the interaction between thrombin (or other PAR3 activating compounds) and PAR3. The teaching of Coughlin *et al.*, is limited to methods involving extracellular ligands and does not involve G protein/G protein coupled receptor interactions. The reference does not even refer to, mention or hint at the possibility of affecting G protein/G protein coupled receptor interactions. It does not discuss or even suggest methods involving a peptide library based on a native binding sequence in any binding molecule for screening in comparison to the native binding sequence, even for extracellular ligands, and does not mention, suggest, or even hint at a method which is capable of discovering molecules that specifically affect a specific G protein coupled receptor interaction intracellularly. The teachings are confined to traditional ligand binding assays using the PAR3 receptor and do not even relate to the invention claimed here, which does not involve receptor agonists or antagonists that mimic or block a naturally-occurring activating ligand.

The Gilchrist *et al.* reference is cited as a secondary reference to cure the deficiencies of the Coughlin *et al.* disclosures. This reference teaches that the receptor-G protein interface is a possible target for inhibition of G protein coupled receptor activation and that future studies will assess whether inhibitors of this interface can be found or designed. Gilchrist *et al.* also disclose certain Gα peptide analogs that can disturb the molecular interface occurring between a G protein and a G protein coupled receptor. However, there is no disclosure in Gilchrist *et al.* of methodology on how to use these

Gα peptide analogs to identify specific inhibitors of G protein coupled receptors.

To make out a prima facie case of obviousness against a claim, the Office must meet three criteria: (1) the cited prior art references must teach or suggest each and every element of the rejected claim, (2) there must be motivation to combine or modify what is fairly disclosed in the references to achieve the claimed invention and (3) there must be a reasonable expectation of success. M.P.E.P. §2143. Applicants respectfully submit that the Office cannot make out a prima facie case of obviousness with respect to the presently claimed invention based on the Coughlin *et al.* and Gilchrist *et al.* references.

Neither of the references disclose a method of identifying a G protein coupled receptor signaling inhibitor, and certainly do not enable such a method. Even in combination, the method of the invention is not disclosed or suggested by these teachings. The references do not disclose or suggest a peptide library based on a native G protein peptide sequence that binds to the G protein coupled receptor on an intracellular location, they do not disclose or suggest screening such a library to identify peptides that bind to the G protein coupled receptor with higher affinity than that of the native G protein peptide sequence, they do not disclose or suggest screening a library of compounds for binding to the G protein coupled receptor in competition with such a peptide and they do not disclose or suggest identifying compounds with higher affinity than the peptide as a G protein coupled receptor signaling inhibitor. Therefore, at the very least, the Coughlin *et al.* and Gilchrist *et al.* references, when taken together, do not disclose or suggest the steps of the claimed method. Therefore, the first requirement is not met. The references do not teach this method and do not even suggest this method.

If the method of Coughlin *et al.* were adapted to use the sequence taught by Gilchrist *et al.*, the most that could be accomplished would be an assay to determine whether G protein-based peptides bind as traditional agonists or antagonists to the extracellular ligand-binding domain of PAR3. The methods of Coughlin *et al.* involve incubation of whole cells expressing PAR3 (see Example 7) with candidate peptides. Under these conditions, intracellular binding of the peptides would not be possible and no binding to the extracellular domain would be expected. See Fowlkes *et al.*, p. 6, ll. 22-23, which teaches that peptides in general do not transit cell membranes. Additional embodiments discussed at cols. 17-18 of Coughlin *et al.* relate to studies using extracellular domains of PAR3 for binding. Again, an intracellular binding compound would not be expected to bind under these assay conditions. The assays provided by Coughlin *et al.* therefore would not be able to work to achieve the invention even if the teachings were combined. The teachings are not compatible. There could not be any motivation to combine these teachings since the Coughlin *et al.* methods are specifically designed to screen for traditional extracellular ligands and do not even permit intracellular binding of peptides to occur. The second criterion therefore has not been met.

Because the methods of Coughlin *et al.* are not compatible with the G protein-based peptides of the invention and cannot be used to assay the G protein/G protein coupled receptor interface which is described by Gilchrist *et al.*, there would be no expectation that the methods could succeed at achieving the invention claimed here. Therefore, the third criterion is not met.

In summary, the Office cannot meet even one of the necessary criteria to make out a prima facie case of obviousness against the claimed invention. The method steps recited in the claims

are not taught or suggested by either reference alone or in combination. The methods of Coughlin *et al.* cannot be combined with the G protein peptide taught by Gilchrist *et al.*, removing any possible motivation to combine the references, and the methods of Coughlin *et al.* cannot function according to the invention with intracellular-binding G protein sequences, removing any hope of success. Applicants respectfully request that the rejection based or obviousness under 35 U.S.C. §103(a) over Coughlin *et al.* in view of Gilchrist *et al.* be withdrawn.

Fowlkes *et al.* are cited as disclosing "the same method as Coughlin." The Office specifically refers to teaching on page 128 and in the claims. To the extent that the Office's assertions regarding the teachings of Fowlkes *et al.* are true, the discussion above relating to Coughlin *et al.* is equally applicable here. For these reasons above, Applicants request that the rejection based on the combination of Fowlkes *et al.* and Gilchrist *et al.* be withdrawn.

Fowlkes *et al.*, like Coughlin *et al.*, relates to ligands for cellular receptors and enzymes, etc. and does not even mention G protein/G protein coupled receptor interactions on the intracellular face of the receptor. There is no hint or suggestion in Fowlkes *et al.* that the intracellular face of a G protein coupled receptor could be assayed for interaction with G protein-based sequences or even in fact that this type of interaction even exists. Applicants here do not claim to have invented binding assays in general or libraries per se, such as those discussed in Fowlkes *et al.*, therefore disclosures related to these methods are not relevant to the claims presented here.

Although the Office has pointed to page 128 (Example 11) for relevant methods, the example on page 128 relates to purified estrogen receptor, a nuclear hormone receptor and not a G protein coupled receptor. The example points out that the nuclear

receptors have at least two biologically relevant sites: the hormone binding pocket and the DNA binding site. They do not have a region that binds to G proteins as they do not belong to the G protein coupled receptor family. The methods on page 128 describe the use of surrogate ligands to identify small molecule agonists/antagonists. These methods, which allowed Fowlkes *et al.* to isolate molecules that bound to the receptor, for example in the estradiol ligand-binding pocket, do not relate to the methods claimed in this application and do not suggest the claimed methods to a skilled artisan. Nor do they provide motivation to combine these methods with the teachings of Gilchrist *et al.*

Nevertheless, even if the methods of Example 11 in Fowlkes *et al.* were combined with the teachings of Gilchrist *et al.* (discussed at length above) regarding a "library from the carboxyl terminus of the Gα submit of the G protein" for screening for binding to adenosine receptor as the Office asserts would be done, the most that would be accomplished is identification of peptides that bound to purified receptor. Therefore, even the combination of these methods (which would not be combined by the skilled artisan since motivation to do so is lacking in the references) does not disclose all limitations of the claims presented here. The methods are not designed to assay G protein/G protein coupled receptor interactions and do not involve sequential use of library screenings to obtain compounds having equal or higher affinity than previously selected peptides which have higher affinity than a native sequence. The "complementary combinatorial libraries" of Fowlkes *et al.* provide a method designed to operate without the need for a native or "natural binding partner." See p. 8, ll. 3-7. Therefore comparisons of affinity to native sequences are not made by Fowlkes *et al.* and are even discouraged. Further, the

"complementary library" used by Fowlkes *et al.* is "[o]ften...less specific in their binding to the ...target protein than are the members of the first library..." See p. 11, ll.35-38. This indicates to the skilled person that the methods described by Fowlkes *et al.* are not designed to and cannot achieve the methods claimed here, thus destroying any possible motivation to combine them, since success would not be reasonably expected.

In summary, the Office cannot meet even one of the criteria necessary to make out a prima facie case of obviousness with respect to Fowlkes *et al.* in view of Gilchrist *et al.* The references do not teach each and every limitation of the claims, the methods would not be combined by the person of skill because no motivation exists to relate the two references' teachings, and expectation of success when combining the incompatible methods does not exist. Applicants therefore request that the Office withdraw the rejection of claims under 35 U.S.C. §103(a) over Fowlkes *et al.* and Gilchrist *et al.*

For reasons discussed above, Applicants request favorable consideration of the application at this time.

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Enclosures:
Substitute Sequence Listing Paper Copy (72 Pages)
Computer Readable form of Substitute Sequence Listing
Inventors' Declaration

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